

REMARKS

Status of the claims

Claims 2 - 10 and 12 - 41 are pending.

Claims 3, 5 - 7, 9, 10, 12 - 15, 18 - 35 and 38 - 41 have been withdrawn from consideration as drawn to non-elected subject matter, with method claims 26 - 35 and 38 - 41 to be considered for rejoinder at such time as allowable composition claims are identified.

Claims 2, 4, 8, 16, 17, 36 and 37 have been examined.

Claims 2 and 8 are rejected.¹ Claims 4, 16, 17, 36 and 37 are allowable if rewritten in independent form to include limitations from all claims from which they respectively depend.

Claims 2 and 30 are amended herein.

Claims 2 (as amended), 4, 8, 16, 17, 36 and 37 are thus presented for further examination.

Objection under 35 U.S.C. §112, ¶ 2

Applicants have amended claim 2 by deleting the term "human" from the phrase "human secretory leukocyte protease inhibitor activity", bringing the claim language into explicit conformity with the Examiner's understanding of applicants' intent.

Rejections under 35 U.S.C. §103

The Examiner rejects claims 2 and 8 under 35 U.S.C. § 103 as having been obvious over AU-B-13288/88 (the "Australian patent"), further in view of Bingle *et al.*, *Thorax* 51:1273 - 1274 ("Bingle"). Applicants respectfully traverse.

¹ Applicants note that the Office Action Summary, at item 6, states that claims 2 and 4 are rejected, and at item 7 recites that claim 4 is objected to. Applicants understand from the body of the office action, however, that claims 2 and 8 are rejected, with claim 4 objected to as depending from rejected claim 2, and have so responded in the body of this paper.

Bingle, a brief, two page, speculative review, suggests that "[i]nhaled recombinant SLPI (rSLPI) could prove beneficial in partnership with α 1-PI in the treatment of a number of inflammatory lung disorders. . . . " "rSLPI has been successfully administered to patients with cystic fibrosis. . . . It is feasible that rSLPI could be used to treat other inflammatory lung disorders which involve NE [neutrophil elastase] including emphysema, bronchiectasis, pulmonary fibrosis, acute lung injury and bronchopulmonary dysplasia. Probably the most effective treatment would entail combining SLPI and α 1-PI. . . . "

It is agreed that Bingle neither teaches nor suggests fusing SLPI to AAT to create the fusion proteins of applicants' claims 2 and 8.

The Examiner suggests, however, that the reference nonetheless provides sufficient motivation to create such fusion proteins, since "Bingle et al. *strongly suggest* that secretory leukocyte protease inhibitor and alpha1-protease inhibitor. . . are the most effective for treatment of . . . inflammatory lung disorders . . . when used in combination."²

As a preliminary, applicants respectfully submit that the qualified and conditional nature of Bingle's actual language -- "*could prove* beneficial", "*feasible that* rSLPI *could be used*", and "[p]robably the most effective *would* entail" -- falls somewhat short of "strongly suggest[ing]" the coadministration of the two protease inhibitors.

And whatever the "strength" of Bingle's suggestion that SLPI be *coadministered* with AAT, applicants respectfully submit that such suggestion would not have motivated the fusion of the two active agents into a single entity.

Fusion obligates the administration of the two agents in fixed, typically 1:1, stoichiometry, on a common dosage schedule, by common route of administration, in common formulation. Nothing in Bingle suggests the desirability of so constraining the clinical administration of these two agents -- if anything, Bingle's comment that SLPI remains potent when oxidized, in contrast to AAT, would suggest that SLPI be less frequently administered, or in lower dosage, than AAT, teaching away from their fusion.

² Office action, page 4 (emphasis added; original emphasis elided).

The Examiner suggests that the Australian patent, said to teach "construction of [a] hybrid serpin that is a fusion protein comprising human secretory leukocyte protease inhibitor,"³ would have provided a reasonable expectation of successfully fusing SLPI and AAT into a single, bifunctional, protease inhibitor.

With respect, the Examiner has misread the reference.

The Australian patent discloses exon-swapped hybrid proteins comprising one or more exons from human leuserpin 2 (hLS2), not SLPI: hLS2 is a 499 amino acid protein encoded by a gene with 5 exons; human secretory leukocyte protease inhibitor is a 132 amino acid protein encoded by a gene having only 2 exons. The GenBank entries for the two proteins are attached, respectively, as Exhibits A and B.

The invention disclosed in the Australian patent is predicated on its inventors' isolation of a genomic clone encoding hLS2 (the cDNA having been previously disclosed), and their discovery that "the hLS2 gene structure corresponds to that of [human] α 1-antitrypsin and or (rat) angiotensinogen in respect of the number and location of the introns." Each of hLS2, human α 1-antitrypsin, and rat angiotensinogen is encoded by a gene having 5 exons interrupted at corresponding locations in the coding sequence by four introns. This correspondence ("analogy") in exon/intron structure "is utilized . . . for the preparation of the hybrid serpins"⁴ by swapping of corresponding exons.

In each case, the hybrid serpin has one each of exons 1, 2, 3, 4, and 5, at least one having been drawn from hLS2.

The term "hybrid serpin" in connection with the present invention is intended to indicate that the protein being dealt with is composed of amino acid blocks which substantially correspond to exons of hLS2 and analogous serpins having the same gene structure, and exhibits proteinase-inhibitory activity.⁵

³ Office action, page 4.

⁴ AU-B-13288/88, p. 2, lines 28 - 31.

⁵ AU-B-13288/88, p. 4, lines 6 - 11 (emphasis added).

"Exon modules . . . according to the invention, [are] assembled . . . in virtually any desired combination **but in the correct relative orientation to one another and in the correct sequence.**"⁶ For example, "Figure 2 shows . . . the construction of a hybrid serpin gene having the exons 1 to 4 of hLS2. . . and having the 3' terminal exon of the human α 1-antitrypsin gene. . . ." ⁷

In no case is a fusion described or suggested that includes other exon structures -- such as fusion of the two exon SLPI protein to any one or more of the five exons of AAT -- or that possesses two different spectra of protease inhibitory activities, such as "alpha 1-antitrypsin protease inhibitor activity and secretory leukocyte protease inhibitor activity" as called for in applicants' claim 2.

The only "bifunctional" proteins described in the Australian patent contains "the activities of angiotensin II and antitrypsin. . . ." ⁸

Angiotensin II is an octapeptide that causes arteriolar vasoconstriction and stimulates aldosterone secretion, playing an important role in the control of blood pressure and fluid balance. It is physiologically derived from angiotensinogen in two steps: cleavage of a decapeptide, angiotensin I, from the N-terminus of angiotensinogen by the enzyme renin, followed by a subsequent cleavage of angiotensin I by angiotensin-converting enzyme. The exon-swapped hybrids disclosed in the Australian patent -- limited as they are to chimeras comprising exons 1 - 5 drawn from hLS2 and either or both of rat angiotensinogen and human AAT -- will include "the activities of angiotensin II and antitrypsin" if the N terminal exons of the hybrid are drawn from rat angiotensinogen and the C terminal exons from AAT.

This is not the SLPI/AAT fusion of applicants' claims 2 and 8.

More generally, providing a *substrate* for proteolytic cleavage by renin is not the provision of a second protease inhibitory activity -- "bifunctional", as used in the reference, is not the provision of two distinct protease inhibitory activities as herein claimed.

⁶ AU-B-13288/88, p. 5, lines 1 - 4 (emphasis added).

⁷ AU-B-13288/88, p. 3, lines 15 - 19.

⁸ AU-B-13288/88, p. 5, lines 24 - 28.

Applicants thus respectfully submit that the Examiner is factually mistaken in asserting that "the Australian document teaches the construction of fusion protein[s] containing SLPI and part of alpha 1-antitrypsin, or any serpin, and strongly suggest construction [of] bifunctional serpins": the patent does not teach SLPI fusions; it does not teach fusions, except in the very limited sense of exon-swapped chimeras drawn from hLS2, rat angiotensinogen, and human AAT; and the patent does not teach "bifunctional" proteins in the sense of providing two types of protease inhibitory activity.

Having thus misconstrued the scope and content of the prior art, the Examiner cannot properly conclude therefrom that the art provided a reasonable expectation of successfully making and using applicants' fusion proteins.

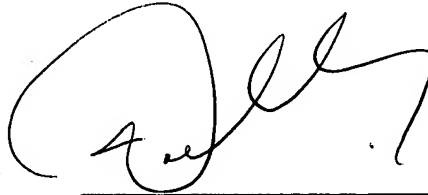
Applicants respectfully submit that the cited art neither provided the motivation to make applicants' invention, nor a reasonable expectation of successfully so doing. The Examiner's *prima facie* case of obviousness is thus unfounded, *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art."), the burden of production has not properly been shifted to applicants, and applicants are entitled, without more, to their claims, *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992).

CONCLUSION

Applicants submit that the present claims are in condition for allowance, and respectfully request that withdrawn method claims be rejoined and examined. If the Examiner believes that any matters remain outstanding, however, applicants respectfully invite the Examiner to call the undersigned to schedule a telephonic interview.

Respectfully submitted,

HELLER EHRMAN WHITE & MCAULIFFE LLP



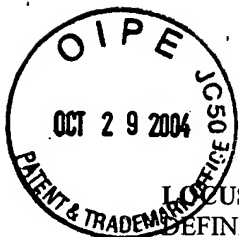
Date: OCTOBER 28, 2004

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Attachments: Exhibit A -- GenBank entry for hLS2
Exhibit B -- GenBank entry for SLPI

Enclosures: Power of Attorney
Statement under 37 C.F.R. § 3.73(b)



EXH. A

LOCUS P05546 499 aa linear PRI 25-OCT-2004
DEFINITION Heparin cofactor II precursor (HC-II) (Protease inhibitor leuserpin
2) (HLS2).
ACCESSION P05546
VERSION P05546 GI:123055
DBSOURCE swissprot: locus HEP2_HUMAN, accession P05546;
class: standard.
created: Nov 1, 1988.
sequence updated: Nov 1, 1991.
annotation updated: Oct 25, 2004.
xrefs: gi: 183907, gi: 183908, gi: 32314, gi: 1335104, gi: 183909,
gi: 183910, gi: 187234, gi: 187236, gi: 106228, pdb accession 1JMJ,
pdb accession 1JMO
xrefs (non-sequence databases): GenewHGNC:4838, MIM142360,
MIM188050, GO0004866, InterProIPR000295, InterProIPR000215,
PfamPF00079, PRINTSPR00780, SMARTSM00093, PROSITEPS00284
KEYWORDS 3D-structure; Blood coagulation; Chemotaxis; Direct protein
sequencing; Disease mutation; Glycoprotein; Heparin-binding;
Plasma; Polymorphism; Repeat; Serine protease inhibitor; Serpin;
Signal; Sulfation; Thrombophilia.
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (residues 1 to 499)
AUTHORS Herzog,R., Lutz,S., Blin,N., Marasa,J.C., Blinder,M.A. and
Tollefsen,D.M.
TITLE Complete nucleotide sequence of the gene for human heparin cofactor
II and mapping to chromosomal band 22q11
JOURNAL Biochemistry 30 (5), 1350-1357 (1991)
MEDLINE 91120782
PUBMED 1671335
REMARK SEQUENCE FROM N.A.
REFERENCE 2 (residues 1 to 499)
AUTHORS Blinder,M.A., Marasa,J.C., Reynolds,C.H., Deaven,L.L. and
Tollefsen,D.M.
TITLE Heparin cofactor II: cDNA sequence, chromosome localization,
restriction fragment length polymorphism, and expression in
Escherichia coli
JOURNAL Biochemistry 27 (2), 752-759 (1988)
MEDLINE 88163663
PUBMED 2894851
REMARK SEQUENCE FROM N.A.
REFERENCE 3 (residues 1 to 499)
AUTHORS Ragg,H.
TITLE A new member of the plasma protease inhibitor gene family
JOURNAL Nucleic Acids Res. 14 (2), 1073-1088 (1986)
MEDLINE 86120356
PUBMED 3003690
REMARK SEQUENCE OF 19-499 FROM N.A.
REFERENCE 4 (residues 1 to 499)
AUTHORS Inhorn,R.C. and Tollefsen,D.M.
TITLE Isolation and characterization of a partial cDNA clone for heparin
cofactor II
JOURNAL Biochem. Biophys. Res. Commun. 137 (1), 431-436 (1986)
MEDLINE 86242236

PUBMED 3755044
 REMARK SEQUENCE OF 333-499 FROM N.A.
 REFERENCE 5 (residues 1 to 499)
 AUTHORS Griffith,M.J., Noyes,C.M., Tyndall,J.A. and Church,F.C.
 TITLE Structural evidence for leucine at the reactive site of heparin cofactor II
 JOURNAL Biochemistry 24 (24), 6777-6782 (1985)
 MEDLINE 86077723
 PUBMED 3907702
 REMARK SEQUENCE OF 20-52 AND 464-499.
 REFERENCE 6 (residues 1 to 499)
 AUTHORS Ragg,H. and Preibisch,G.
 TITLE Structure and expression of the gene coding for the human serpin HLS2
 JOURNAL J. Biol. Chem. 263 (24), 12129-12134 (1988)
 MEDLINE 88298901
 PUBMED 2841345
 REMARK SEQUENCE OF 1-119 FROM N.A.
 REFERENCE 7 (residues 1 to 499)
 AUTHORS Church,F.C., Pratt,C.W. and Hoffman,M.
 TITLE Leukocyte chemoattractant peptides from the serpin heparin cofactor II
 JOURNAL J. Biol. Chem. 266 (2), 704-709 (1991)
 MEDLINE 91093260
 PUBMED 1985958
 REMARK SEQUENCE OF 58-85.
 REFERENCE 8 (residues 1 to 499)
 AUTHORS Van Deerlin,V.M. and Tollefsen,D.M.
 TITLE The N-terminal acidic domain of heparin cofactor II mediates the inhibition of alpha-thrombin in the presence of glycosaminoglycans
 JOURNAL J. Biol. Chem. 266 (30), 20223-20231 (1991)
 MEDLINE 92041850
 PUBMED 1939083
 REMARK FUNCTION OF N-TERMINAL ACIDIC DOMAIN.
 REFERENCE 9 (residues 1 to 499)
 AUTHORS Blinder,M.A. and Tollefsen,D.M.
 TITLE Site-directed mutagenesis of arginine 103 and lysine 185 in the proposed glycosaminoglycan-binding site of heparin cofactor II
 JOURNAL J. Biol. Chem. 265 (1), 286-291 (1990)
 MEDLINE 90094412
 PUBMED 2104620
 REMARK MUTAGENESIS OF ARG-122 AND LYS-204.
 REFERENCE 10 (residues 1 to 499)
 AUTHORS Blinder,M.A., Andersson,T.R., Abildgaard,U. and Tollefsen,D.M.
 TITLE Heparin cofactor II Oslo. Mutation of Arg-189 to His decreases the affinity for dermatan sulfate
 JOURNAL J. Biol. Chem. 264 (9), 5128-5133 (1989)
 MEDLINE 89174798
 PUBMED 2647747
 REMARK VARIANT HCF-II DEFICIENCY HIS-208.
 REFERENCE 11 (residues 1 to 499)
 AUTHORS Cargill,M., Altshuler,D., Ireland,J., Sklar,P., Ardlie,K., Patil,N., Shaw,N., Lane,C.R., Lim,E.P., Kalyanaraman,N., Nemesh,J., Ziaugra,L., Friedland,L., Rolfe,A., Warrington,J., Lipshutz,R., Daley,G.Q. and Lander,E.S.
 TITLE Characterization of single-nucleotide polymorphisms in coding

regions of human genes
JOURNAL Nat. Genet. 22 (3), 231-238 (1999)
MEDLINE 99318093
PUBMED 10391209
REMARK VARIANT HCF-II DEFICIENCY HIS-208, AND VARIANTS THR-7 AND MET-442.
REFERENCE 12 (residues 1 to 499)
AUTHORS Cargill,M., Altshuler,D., Ireland,J., Sklar,P., Ardlie,K.,
Patil,N., Shaw,N., Lane,C.R., Lim,E.P., Kalyanaraman,N., Nemesh,J.,
Ziaugra,L., Friedland,L., Rolfe,A., Warrington,J., Lipshutz,R.,
Daley,G.Q. and Lander,E.S.
JOURNAL Nat. Genet. 23, 373-373 (1999)
PUBMED 10545957
REMARK ERRATUM.
COMMENT -----

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[FUNCTION] Thrombin inhibitor activated by the glycosaminoglycans, heparin or dermatan sulfate. In the presence of the latter, HC-II becomes the predominant thrombin inhibitor in place of antithrombin III (AT-III). Also inhibits chymotrypsin, but in a glycosaminoglycan-independent manner.

[FUNCTION] Peptides at the N-terminal of HC-II have chemotactic activity for both monocytes and neutrophils.

[TISSUE SPECIFICITY] Expressed predominantly in liver.

[DOMAIN] The N-terminal acidic repeat region mediates, in part, the glycosaminoglycan-accelerated thrombin inhibition.

[DISEASE] Defects in SERPIND1 are the cause of heparin cofactor II deficiency (HCF-II deficiency) [MIM:142360, 188050]. HCF-II deficiency is a form of thrombophilia [MIM:188050], an autosomal dominant disorder in which affected individuals are prone to develop serious spontaneous thrombosis.

[SIMILARITY] Belongs to the serpin family.

FEATURES	Location/Qualifiers
source	1..499
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	/db_xref="taxon:9606"
gene	1..499
	/gene="SERPIND1"
	/note="synonym: HCF2"
Protein	1..499
	/gene="SERPIND1"
	/product="Heparin cofactor II precursor"
Region	1..19
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	/region_name="Signal"
Region	7
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	/region_name="Variant"
	/note="A -> T (in dbSNP:5905). /FTId=VAR_011746."
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	/region_name="Mature chain"

/note="Heparin cofactor II."
 Region 49
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 /note="Missing (in Ref. 5)."
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 Region 60
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 /region_name="Variant"
 /note="H -> P (in dbSNP:165867). /FTId=VAR_011747."
 Region 68..79
 /gene="SERPIND1"
 /region_name="Domain"
 /note="Chemotactic activity."
 Region 73..97
 /gene="SERPIND1"
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 /note="2 X 11 AA approximate repeats, Asp/Glu- rich
 (acidic) (hirudin-like)."
 Region 73..83
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 /note="1."
 Site 79
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 Region 87..97
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 Region 118..119
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 /region_name="Hydrogen bonded turn"

Region 122..142
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 /site_type="mutagenized"
 /note="R->Q: Greatly reduced thrombin inhibition. Normal glycosaminoglycan affinity."
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 /note="SERPIN"
 /db_xref="CDD:5278"
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 Region 147..148
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 Region 151..153
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 Region 155..165
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 Region 166..168
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 Region 171..180
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 Region 181..182
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 Region 183..189
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Region 192..212
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 /note="Glycosaminoglycan-binding site."

Region 195..210
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 /region_name="Helical region"

Site 204
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 /note="K->N: Reduced heparin- and no dermatan sulfate-activated inhibition."

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 /site_type="mutagenized"
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Region 228..229
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Region 234..244
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 /region_name="Helical region"

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Region 256..269
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Region 270..272
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Region 277..278
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Region 283..284
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 Region 305..307
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 Region 309..314
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 Region 320..337
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 Region 338..341
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 Region 342..349
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 Region 350..352
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 Region 375..384
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 Region 386..395
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 Region 403..404
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 Region 406..412
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 Region 413

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Region    420..421
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Region    425..427
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Region    434..445
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        /region_name="Beta-strand region"
Region    442
        /gene="SERPIND1"
        /region_name="Variant"
        /note="T -> M (in dbSNP:5904). /FTId=VAR_011749."
Region    449
        /gene="SERPIND1"
        /region_name="Beta-strand region"
Region    460..462
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        /region_name="Beta-strand region"
Site      463..464
        /gene="SERPIND1"
        /site_type="unclassified"
        /note="Reactive bond (By similarity)."
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Region 468..470

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        /gene="SERPIND1"
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Region    475..481
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Region    482..485
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        /region_name="Hydrogen bonded turn"
Region    483
        /gene="SERPIND1"
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Region 486..493

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Region 496..497

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Region    499
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```

ORIGIN

1 mkhslnalli fliitsawgg skgpldqlek ggetaqsadp qweqlnnknl smpllpadfh
61 kentvndwi pegeedddyl dlekifsedd dyidivdsls vsptdsdvsd gnilqlfhgk
121 sriqrlniln akfafnlyrv lkdqyntfdn ifiapvgist amgmislglk getheqvhsi
181 lhfkdfvnas skyeittihn lfrklthrlf rrnfgytls vndlyiqkqf pilldfktkv
241 reyyfaeqi adfsdpafis kttnhimklt kglikdalen idpatqmmil nciyfkgswv
301 nkfpvemthn hnfrlnerev vkvsmmqtkg nflaandqel dcdilqleyv ggismlivvp
361 hkmsgmktle aqltprvver wqksmtnrtr evllpkfkle knynlveslk lmgirmldk
421 ngnmagisdq riaidlfkhq gtitvneegt qattvtvgf mplstqvrft vdrpfliiy
481 ehrtscellfm grvanpsrs

//



EXH. B

LOCUS P03973 132 aa linear PRI 25-OCT-2004
DEFINITION Antileukoproteinase 1 precursor (ALP) (HUSI-1) (Seminal proteinase inhibitor) (**Secretory leukocyte protease inhibitor**) (BLPI) (Mucus proteinase inhibitor) (MPI) (WAP four-disulfide core domain protein 4) (Protease inhibitor WAP4).
ACCESSION P03973
VERSION P03973 GI:113636
DBSOURCE swissprot: locus ALK1_HUMAN, accession P03973;
class: standard.
extra accessions:P07757,created: Oct 23, 1986.
sequence updated: Oct 1, 1989.
annotation updated: Oct 25, 2004.
xrefs: gi: 28638, gi: 28639, gi: 4378758, gi: 4378759, gi: 11418457, gi: 6630766, gi: 18088404, gi: 18088405, gi: 36485, gi: 758101, gi: 36490, gi: 36491, gi: 1070529
xrefs (non-sequence databases): HSSPP19957, GenewHGNC:11092, MIM107285, GO0004866, InterProIPR008198, InterProIPR008197, PfamPF00095, PRINTSPR00003, ProDomPD001224, SMARTSM00217, PROSITEPS00317
KEYWORDS Direct protein sequencing; Repeat; Serine protease inhibitor; Signal.
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (residues 1 to 132)
AUTHORS Heinzl,R., Appelhans,H., Gassen,G., Seemuller,U., Machleidt,W., Fritz,H. and Steffens,G.
TITLE Molecular cloning and expression of cDNA for human antileukoprotease from cervix uterus
JOURNAL Eur. J. Biochem. 160 (1), 61-67 (1986)
MEDLINE 87030258
PUBMED 3533531
REMARK SEQUENCE FROM N.A.
REFERENCE 2 (residues 1 to 132)
AUTHORS Stetler,G., Brewer,M.T. and Thompson,R.C.
TITLE Isolation and sequence of a human gene encoding a potent inhibitor of leukocyte proteases
JOURNAL Nucleic Acids Res. 14 (20), 7883-7896 (1986)
MEDLINE 87040761
PUBMED 3640338
REMARK SEQUENCE FROM N.A.
TISSUE=Parotid gland
REFERENCE 3 (residues 1 to 132)
AUTHORS Si-Tahar,M., Merlin,D., Sitaraman,S. and Madara,J.L.
TITLE Direct Submission
JOURNAL Submitted (??-DEC-1998)
REMARK SEQUENCE FROM N.A.
TISSUE=Intestine
REFERENCE 4 (residues 1 to 132)
AUTHORS Deloukas,P., Matthews,L.H., Ashurst,J., Burton,J., Gilbert,J.G., Jones,M., Stavrides,G., Almeida,J.P., Babbage,A.K., Bagguley,C.L., Bailey,J., Barlow,K.F., Bates,K.N., Beard,L.M., Beare,D.M., Beasley,O.P., Bird,C.P., Blakey,S.E., Bridgeman,A.M., Brown,A.J., Buck,D., Burrill,W., Butler,A.P., Carder,C., Carter,N.P., Chapman,J.C., Clamp,M., Clark,G., Clark,L.N., Clark,S.Y.,

EXHIBIT B

Clee,C.M., Clegg,S., Cobley,V.E., Collier,R.E., Connor,R.,
 Corby,N.R., Coulson,A., Coville,G.J., Deadman,R., Dhami,P.,
 Dunn,M., Ellington,A.G., Frankland,J.A., Fraser,A., French,L.,
 Garner,P., Grafham,D.V., Griffiths,C., Griffiths,M.N., Gwilliam,R.,
 Hall,R.E., Hammond,S., Harley,J.L., Heath,P.D., Ho,S., Holden,J.L.,
 Howden,P.J., Huckle,E., Hunt,A.R., Hunt,S.E., Jekosch,K.,
 Johnson,C.M., Johnson,D., Kay,M.P., Kimberley,A.M., King,A.,
 Knights,A., Laird,G.K., Lawlor,S., Lehvaslaiho,M.H., Leversha,M.,
 Lloyd,C., Lloyd,D.M., Lovell,J.D., Marsh,V.L., Martin,S.L.,
 McConnachie,L.J., McLay,K., McMurray,A.A., Milne,S., Mistry,D.,
 Moore,M.J., Mullikin,J.C., Nickerson,T., Oliver,K., Parker,A.,
 Patel,R., Pearce,T.A., Peck,A.I., Phillimore,B.J.,
 Prathalingam,S.R., Plumb,R.W., Ramsay,H., Rice,C.M., Ross,M.T.,
 Scott,C.E., Sehra,H.K., Shownkeen,R., Sims,S., Skuce,C.D.,
 Smith,M.L., Soderlund,C., Steward,C.A., Sulston,J.E., Swann,M.,
 Sycamore,N., Taylor,R., Tee,L., Thomas,D.W., Thorpe,A., Tracey,A.,
 Tromans,A.C., Vaudin,M., Wall,M., Wallis,J.M., Whitehead,S.L.,
 Whittaker,P., Willey,D.L., Williams,L., Williams,S.A., Wilming,L.,
 Wray,P.W., Hubbard,T., Durbin,R.M., Bentley,D.R., Beck,S. and
 Rogers,J.

TITLE The DNA sequence and comparative analysis of human chromosome 20
 JOURNAL Nature 414 (6866), 865-871 (2001)
 MEDLINE 21638749
 PUBMED 11780052
 REMARK SEQUENCE FROM N.A.
 REFERENCE 5 (residues 1 to 132)

AUTHORS Strausberg,R.L., Feingold,E.A., Grouse,L.H., Derge,J.G.,
 Klausner,R.D., Collins,F.S., Wagner,L., Shenmen,C.M., Schuler,G.D.,
 Altschul,S.F., Zeeberg,B., Buetow,K.H., Schaefer,C.F., Bhat,N.K.,
 Hopkins,R.F., Jordan,H., Moore,T., Max,S.I., Wang,J., Hsieh,F.,
 Diatchenko,L., Marusina,K., Farmer,A.A., Rubin,G.M., Hong,L.,
 Stapleton,M., Soares,M.B., Bonaldo,M.F., Casavant,T.L.,
 Scheetz,T.E., Brownstein,M.J., Usdin,T.B., Toshiyuki,S.,
 Carninci,P., Prange,C., Raha,S.S., Loquellano,N.A., Peters,G.J.,
 Abramson,R.D., Mullahy,S.J., Bosak,S.A., McEwan,P.J.,
 McKernan,K.J., Malek,J.A., Gunaratne,P.H., Richards,S.,
 Worley,K.C., Hale,S., Garcia,A.M., Gay,L.J., Hulyk,S.W.,
 Villalon,D.K., Muzny,D.M., Sodergren,E.J., Lu,X., Gibbs,R.A.,
 Fahey,J., Helton,E., Kettelman,M., Madan,A., Rodrigues,S.,
 Sanchez,A., Whiting,M., Madan,A., Young,A.C., Shevchenko,Y.,
 Bouffard,G.G., Blakesley,R.W., Touchman,J.W., Green,E.D.,
 Dickson,M.C., Rodriguez,A.C., Grimwood,J., Schmutz,J., Myers,R.M.,
 Butterfield,Y.S., Krzywinski,M.I., Skalska,U., Smailus,D.E.,
 Schnerch,A., Schein,J.E., Jones,S.J. and Marra,M.A.

TITLE Generation and initial analysis of more than 15,000 full-length
 human and mouse cDNA sequences
 JOURNAL Proc. Natl. Acad. Sci. U.S.A. 99 (26), 16899-16903 (2002)
 MEDLINE 22388257
 PUBMED 12477932
 REMARK SEQUENCE FROM N.A.
 TISSUE=Liver

REFERENCE 6 (residues 1 to 132)
 AUTHORS Seemuller,U., Arnhold,M., Fritz,H., Wiedenmann,K., Machleidt,W.,
 Heinzl,R., Appelhans,H., Gassen,H.G. and Lottspeich,F.
 TITLE The acid-stable proteinase inhibitor of human mucous secretions
 (HUSI-I, antileukoprotease). Complete amino acid sequence as

revealed by protein and cDNA sequencing and structural homology to whey proteins and Red Sea turtle proteinase inhibitor

JOURNAL FEBS Lett. 199 (1), 43-48 (1986)

MEDLINE 86164996

PUBMED 3485543

REMARK SEQUENCE OF 26-132, AND SEQUENCE OF 26-65 FROM N.A.

REFERENCE 7 (residues 1 to 132)

AUTHORS Thompson,R.C. and Ohlsson,K.

TITLE Isolation, properties, and complete amino acid sequence of human secretory leukocyte protease inhibitor, a potent inhibitor of leukocyte elastase

JOURNAL Proc. Natl. Acad. Sci. U.S.A. 83 (18), 6692-6696 (1986)

MEDLINE 86313644

PUBMED 3462719

REMARK SEQUENCE OF 26-132.

REFERENCE 8 (residues 1 to 132)

AUTHORS Sallenave,J.M. and Ryle,A.P.

TITLE Purification and characterization of elastase-specific inhibitor. Sequence homology with mucus proteinase inhibitor

JOURNAL Biol. Chem. Hoppe-Seyler 372 (1), 13-21 (1991)

MEDLINE 91248412

PUBMED 2039600

REMARK SEQUENCE OF 26-52.

REFERENCE 9 (residues 1 to 132)

AUTHORS Grutter,M.G., Fendrich,G., Huber,R. and Bode,W.

TITLE The 2.5 A X-ray crystal structure of the acid-stable proteinase inhibitor from human mucous secretions analysed in its complex with bovine alpha-chymotrypsin

JOURNAL EMBO J. 7 (2), 345-351 (1988)

MEDLINE 88211544

PUBMED 3366116

REMARK X-RAY CRYSTALLOGRAPHY (2.5 ANGSTROMS).

COMMENT -----

This SWISS-PROT entry is copyright. It is produced through a collaboration between the Swiss Institute of Bioinformatics and the EMBL outstation - the European Bioinformatics Institute. The original entry is available from <http://www.expasy.ch/sprot> and <http://www.ebi.ac.uk/sprot>

[FUNCTION] Acid-stable proteinase inhibitor with strong affinities for trypsin, chymotrypsin, elastase, and cathepsin G. May prevent elastase-mediated damage to oral and possibly other mucosal tissues.

[SUBCELLULAR LOCATION] Secreted.

[TISSUE SPECIFICITY] Mucous fluids.

[DISEASE] The pathologies of several chronic and acute diseases of the respiratory tract involve an imbalance between the proteases of cells involved in inflammatory responses and the inhibitors of these proteases. The inflammation-mediated release of neutrophil elastase in the lungs of patients whose levels of active alpha-1-antiprotease are compromised by genetic background, cigarette smoking, air pollutants, or a combination of all three can result in severe lung damage and a decreased lifespan. The relatively small size of this protein, its lack of glycosylation and its stability make this protein a candidate for use as a therapeutic agent in diseases mediated by leukocyte

elastase-antielastase imbalances.
[SIMILARITY] Contains 2 WAP-type domains.

FEATURES Location/Qualifiers

source 1..132
 /organism="Homo sapiens"
 /db_xref="taxon:9606"

gene 1..132
 /gene="SLPI"
 /note="synonyms: WAP4, WFDC4"

Protein 1..132
 /gene="SLPI"
 /product="Antileukoproteinase 1 precursor"

Region 1..25
 /gene="SLPI"
 /region_name="Signal"

Region 26..132
 /gene="SLPI"
 /region_name="Mature chain"
 /note="Antileukoproteinase 1."

Region 26..83
 /gene="SLPI"
 /region_name="Domain"
 /note="Trypsin inhibitory domain."

Region 31..76
 /gene="SLPI"
 /region_name="Four-disulfide core domains"
 /note="WAP"
 /db_xref="CDD:193"

Region 31..76
 /gene="SLPI"
 /region_name="Domain"
 /note="WAP 1."

Bond bond(35,64)
 /gene="SLPI"
 /bond_type="disulfide"

Bond bond(43,68)
 /gene="SLPI"
 /bond_type="disulfide"

Site 45..46
 /gene="SLPI"
 /site_type="inhibit"
 /note="Inhibitory (P1) (trypsin) (Probable)."

Bond bond(51,63)
 /gene="SLPI"
 /bond_type="disulfide"

Bond bond(57,72)
 /gene="SLPI"
 /bond_type="disulfide"

Region 80..130
 /gene="SLPI"
 /region_name="whey acidic protein-type four-disulfide core domains"
 /note="WAP"
 /db_xref="CDD:5235"

Region 84..132
 /gene="SLPI"

/region_name="Domain"
 /note="Elastase inhibitory domain."
 Region 85..130
 /gene="SLPI"
 /region_name="Domain"
 /note="WAP 2."
 Bond bond(89,118)
 /gene="SLPI"
 /bond_type="disulfide"
 Bond bond(96,122)
 /gene="SLPI"
 /bond_type="disulfide"
 Site 97..98
 /gene="SLPI"
 /site_type="inhibit"
 /note="Inhibitory (P1) (chymotrypsin, elastase)
 (Probable)."
 Bond bond(105,117)
 /gene="SLPI"
 /bond_type="disulfide"
 Bond bond(111,126)
 /gene="SLPI"
 /bond_type="disulfide"

ORIGIN

1 mkssglfpfl vllalgtlap wavegsgksf kagvcppkks aqclrykkpe cqsdwqcpqk
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 121 megkscvspv ka